Now, we're going to go take a look at antibodies and immunoglobulin receptors in context, the context of their overarching family. That is there is a whole huge bunch of proteins that contain similarities to antibodies immunoglobulin receptors and they're part of what's called the immunoglobulin super family. They have immune functions but they also have a variety of cell to cell signaling functions as well. So, what puts you in this family? Well, you have an immunoglobulin domain. Well, that sounds like circular reasoning, but what is an immunoglobulin domain? So, what I am doing here is I have kind of colored this sort of super pipe cleaner in a way that's going to show you a protein peptide domain wrapping up to form an immunoglobulin domain. Now, if you look at this protein peptide model, you can see that some of them are colored kind of blue and some of them this sort of orangey color. Well, the blue sides represent amino acid side chains that are hydrophilic and like to interact with water. The yellow ones are hydrophobic and they like to avoid water, and this causes this peptide tie to fold up into a beta-pleated sheet. Okay? So, when it does that it's going to put the R-group side by side to make a structure like this. Now, furthermore, because these amino acids are hydrophobic and these are hydrophilic, the whole structure comes together like a compact lump. So, here you have one part of the protein going in, going back and forth, back and forth and then coming out again often into another immunoglobulin domain. In this case, the whole domain will be stabilized by a disulfide bond which in this one I am illustrating with a rubber band. So, when we talk about an immunoglobulin domain, we are talking about a region of the protein where the peptide has folded back up in this fan folded arrangement. So, that the hydrophilic parts are inside hydrophobic, excuse me, hydrophobic parts are inside, hydrophilic parts are outside and it's stabilized with a disulfide bond. Now, we can represent this immunoglobulin domain by drawing out the whole thing every single time, but people don't generally tend to want to bother to do that. So, they will illustrate the immunoglobulin domain sometimes by just drawing a lump. So, here would be a lump, here would be one of them, and here would be another one. If we're doing a line drawing of the peptide, we do something that looks like the capital letter C. So, if you see a peptide that does this, and they'll show the disulfide linkages like this, that's another shorthand way of illustrating this domain. Notice, we have three different models so far of the domain. One that I put together with pipe cleaners in 3D, one that I've drawn very casually as a lump, one that I've drawn in a sort of really standard convention that looks nothing like, in terms of spatial relationships, a real immunoglobulin domain but yet serves very well for shorthand universally recognized. In addition to that, I have a model of an antibody in which I have done another version of representing these immunoglobulin domains. Here I have, this is made up here's one, here's one, here's one, here's one. There's a whole bunch of domains on this and you can see that the peptide, which is what this part is for, goes back and forth. I have two cute little sequence here that are designed to represent the disulfide bond. There's a further kind of cute way of representing these and that is, they are sometimes called bread and butter sandwich domains. So, here I have a bread and butter sandwich with a toothpick. The bread represents the hydrophilic outer R-groups of the domain, the butter represents the internal parts of the domain, the toothpick is the disulfide bond. Okay, it's quite a good model for an immunoglobulin domain. Here is an antibody with immunoglobulin domains and that's kind of what you think about when you think about these kinds of proteins. However, an antibody is really an unusual member of the family, kind of like your crazy uncle. Because most members of this family have attached at their C-terminal ends a membrane spanning region, which allows them to be anchored in the plasma membrane. So, a typical immunoglobulin protein in the subfamily has one or more of these immunoglobulin domains. Often, other domains as well and in addition to that is typically embedded in the plasma membrane and attached to it with this part sticking out. So, now I'm going to tell you a story. Like any story, well, maybe some of the details might not be quite right but if this is something that happened 600 million years ago. If any of you have ever served on a jury, you can know that people will often have slightly different versions of things that happened less than two years ago. But there's a general consensus that 600 million years ago, the earth was pretty much frozen solid. This of course had very profound implications on living organisms. The earth had actually gone

through a series of freezes and melts but 600 years ago, the oceans were all frozen to a depth of probably a mile, couple of kilometers. The land masses were all frozen over and well, how did anything live through that? Well, deep down in the ocean we have ocean vents, places where geological activity causes magma and other materials to be vented from underneath the crust of the earth. Even today there are communities that survive in the depths of the ocean deep in the dark around these vents. They would still have been in ranges of temperatures similar to those today. So, they would have been little dots of living communities at the seafloor and not much else above it. Probably, there still would have been places like around Yellowstone, where you have volcanic activity at the surface of the earth. But in general, those again, would be small and scattered communities and they wouldn't have had a whole lot of variety or living organisms. So, this is life of clinging to survival while things are frozen over. While things are frozen over however, the volcanoes continue to spew out CO2 and eventually the concentration of carbon dioxide in the atmosphere rises to the point where you get a runaway greenhouse effect. So, while earth is frozen over, the average temperature is about minus 50 degrees centigrade. When you suddenly switch to a runaway greenhouse effect it's thought that the earth very rapidly warmed to plus 50 degrees centigrade. Which is uncomfortably hot indeed, body temperature is about 37 degrees centigrade. So, this is sometimes called the Great Freeze Fry. We went from very cold temperatures, which essentially placed all of the earth's living systems in these protected warm environments, to something that was very hot. That of course would have been hardest on the surface of the earth and might have finished off even a lot of the things that were hanging out around hot water vents and what have you. But in any event, what happened during the Great Freeze Fry is that most of life was killed off. The little that was left had very little competition once the earth settled down to an appropriate temperature. So, the earth went into this freeze, it went into this fry and then it settled down at a temperature not terribly different from what we have today. Now, what that did was resulted in the melting of the oceans and allowed organisms to expand to the seashore where most of the nutrients tend to be, and even up onto the land. So, what seems to have happened in this period is that evolution was almost on court like a jack in the box. That is you had all of these organisms around and all of a sudden there was this huge variety of niches that opened up across the world and organisms could experiment and not have a lot of competition. So, if they didn't do things too quickly or too correctly, then they didn't necessarily get eaten immediately. So, we think that during this period of time, we started out with things that worked simple and colonial. Relatively simple colonial algae, relatively simple things that are sort of colonial like a sponge. From these antecedents, we had this huge radiation of different forms. In this period of time, the signals that sponges used to make their relatively simple structures seems to have been accepted and used to make more complex ones. For example, sponges have something that's very much like collagen, and today we have collagen as being the base of all epithelial tissues. We find vastly different versions of it helping to produce different structures. A sponge also has cell to cell recognition molecules and many of those are in the immune super globulin family. So, if I take a sponge, and I run it through a sieve, and I have a whole bunch of different cells and I wait. Those cells will use those cell recognition molecules to come back together and reconstruct the sponge. Now, you wouldn't want to try this on your baby brother. Okay? Because of course, we have a vastly more complicated array of recognition molecules and they have to be kind of turned on in sequences we develop. But, those immunoglobulin recognition molecules have their roots in the period of time before the Great Freeze Fry and they were used for cell to cell recognition and some of them still are. Today as we go into antibodies, we're going to see a version of that, that is used to tell that my cell should match up with another one, but it's used to identify things that are not you, that are not self. So, instead of using it for self to self, it's now used for self not-self. Another principle of these molecules is almost all of these recognition molecules are embedded in the cell membrane. But we're going to look at one version, the antibody that is soluble, and is released into solution to defend yourself as a soluble molecule. So, let's go into that now and start looking in detail at the immunoglobulin super family and what its members are doing for you today.